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cont.

contacting the supernatant with a second liquid comprising a second nucleic acid binding solid phase, in the presence of a chaotropic agent and divalent positive ions and in the absence of material containing alcohol groups, wherein the second liquid has a composition such that the resulting mixture of supernatant and second liquid allows for binding of the single stranded nucleic acid to the second solid phase.

Please cancel claims 32-37 without prejudice.

REMARKS

Claims 16-21 and 28-44 are pending in this application. Claims 32-37 are canceled herein without prejudice to the filing of a continuation application for further prosecution. Claims 16, 38 and 44 are amended herein for clarity to more particularly define the invention. Support for these amendments is found in the language of the original claims and throughout the specification, as set forth below. It is believed that no new matter is added by these amendments. In light of these amendments and the following remarks, applicants respectfully request reconsideration of the pending application, entry of these amendments and allowance of the pending claims to issue.

I. Rejection under 35 U.S.C. § 103(a)

The Office Action states that claims 32-37 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Hartley et al. in view of Mullis et al. and Sambrook et al. Specifically, the Office Action states that applicants have argued that Hartley et al. fails to provide teachings for the primer having a random hybridization sequence and an amplification motif and also does not teach that the amplification motif is a specific sequence that may be utilized in further amplification steps. The Examiner replies that, based on the definition of the amplification motif defined in the specification and explained on page 7, any nucleic acid primer will have an amplification motif and any

amplified nucleic acid sequence will be further amplified by a primer which binds to the amplification motif. The Office Action concludes that therefore, applicants' arguments are not persuasive and the rejection is maintained.

Claims 32-37 are canceled herein without prejudice, thereby rendering this rejection moot. Applicants therefore respectfully request its withdrawal.

II. Rejection under 35 U.S.C. § 112, second paragraph

The Office Action states that claims 16-21, 28-31 and 38-44 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the invention. Specifically, the Office Action states that claims 16-21, 28-31 and 38-44 are vague and indefinite because of the language "preferentially" in claims 16, 28, 38 and 44 and that it is unclear whether or not the double stranded nucleic acid binds to the solid phase. The Examiner requests clarification.

Claims 16, 38 and 44 are amended herein to delete the term preferentially. Thus, it is clear from the language of the amended claims that the double stranded nucleic acid binds to the solid phase. It is believed that this amendment to the claims overcomes this rejection and applicants respectfully request its withdrawal.

III. Rejection under 35 U.S.C. § 102(b)

The Office Action states that claims 16-21, 28-31 and 38-44 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Bastian et al. Specifically, the Office Action states that Bastian et al. discloses a method of separating nucleic acid mixtures into their double stranded and single stranded fraction and that all nucleic acids are simultaneously adsorbed in a mineral substrate, then separated by fractional elution into double stranded and single stranded nucleic acids, or double stranded and single stranded nucleic acids of a sample are selectively adsorbed in a mineral substrate. The Office Action further states

that Bastian et al. teaches that the double stranded nucleic acid predominantly binds to the first mineral support and after optionally performed washings steps, can be eluted under conditions of low ionic strength or with water and that the non-adsorbed single-stranded nucleic acids collected are subsequently adjusted and can be adsorbed to a second mineral support and become eluted under conditions of low ionic strength or with water. The Office Action goes on to describe the teachings of Bastian et al. as including a treatment condition containing a chaotropic substance and a mineral support consisting of porous or non-porous metal oxides, silica gel or glass and a particle size of 0.1 μm to 1000 μm. The Office Action also states that Bastian et al. teaches that for binding double stranded nucleic acid to mineral supports, the solution contains guanidinium thiocyanate with a concentration of 1 to 8 M and EDTA with a concentration of from 5 mM to 200 mM and that magnesium chloride in a concentration of from 0.1 to 10 M may also be used in combination for lysing or binding the sources containing nucleic acids and that the complexes comprise alkaline earth metal ions bound to EDTA. From these teachings, the Examiner concludes that the limitations of claims 16-21, 28-31 and 38-44 are anticipated by Bastian et al.

Applicants wish to point out that the Bastian et al. patent and PCT publication are improperly recited in a 35 U.S.C. § 102(b) rejection and that the proper rejection based on these documents is under 35 U.S.C. § 102(a). In particular, the Bastian et al. PCT publication, upon which the present rejection is based, was published on August 17, 1995 and the priority date for the instant application is February 14, 1996. Therefore, the cited art was published within one year of the priority date of the present application and a 35 U.S.C. § 102(b) rejection would not apply.

The Bastian et al. reference does not anticipate the claimed invention. Specifically, applicants point out that the invention set forth in the Bastian et al. patent and PCT publication is based on the discovery by Bastian et al. that variations in the concentration of materials containing alcohol groups in a binding solution allowed for the

differential binding of single stranded nucleic acid or double stranded nucleic acid to a solid support. That this is the discovery of the Bastian et al. invention is set forth in the U.S. patent in column 4, lines 17-43, wherein it is stated:

> FIG. 1 shows the binding of single-stranded/double-stranded nucleic acid exemplified by single-stranded RNA and double-stranded DNA. Described here is the RNA/DNA binding from a tissue lysate to a mineral support as a function of the concentration of a material containing alcohol groups (here, ethanol) and a chaotropic substance (here, GTC). Under the condition that the concentration of one of the substances, alcohol or chaotropic substance, is constant, it is found that at a high alcohol concentration and/or amount of chaotropic substance, both types of nucleic acid (RNA/DNA) are bound to the mineral support. If the concentration of one or both substances (alcohol or chaotropic substance) becomes less than a defined value, none of the nucleic acids will bind to the mineral support to any substantial extent. Surprisingly, in between, RNA and DNA will bind to the mineral support to such different extents as can be made use of for the separation of the nucleic acids. Thus, proceeding from cells, and after lysis of the cells with a high concentration of chaotropic substances, the concentrations of chaotropic substance and material containing alcohol groups can be adjusted by subsequent addition of a material containing alcohol groups or a mixture of material containing alcohol groups and water or buffer such that a selective binding of the RNA is achieved while the DNA remains in the breakthrough. In the example according to FIG. 1, concentrations of 1.75 M GTC and 30% by volume of ethanol would be selected in order to achieve a separation of RNA from DNA by fractional binding. (Emphasis added.)

Thus, the teachings of the Bastian et al. patent are clearly directed to methods of separating single stranded nucleic acid from double stranded nucleic acid by altering the concentration of alcohol in the binding solution. This is reflected in every example recited in the Bastian et al. specification, wherein all enabling descriptions of a method of separating single and double stranded nucleic acids include reagents comprising material containing alcohol groups.

Specifically, in column 8, lines 7-12 of the Bastian et al. patent, the following binding reagents are disclosed:

B1 ethanol
B2 n-butanol
B3 isopropanol
B4 70% ethanol in water
B5 5.9 M GTC (guanidinium thiocyanate).

In column 9, line 61 through column 13, line 53 of the Bastian et al. patent, 13 examples are provided. In each example, the single stranded nucleic acid is bound to the solid support by contacting the single stranded nucleic acid with a binding reagent containing alcohol. Specifically, in example 1, a range of alcohol concentrations from 10% to 50% is applied in a binding reagent to a cell lysate while maintaining a constant GTC concentration. It is stated in the Bastian et al. specification in column 10, lines 21-25 that "...the RNA fraction will bind to the mineral support under the conditions described already from ethanol concentrations of greater than 25% whereas the DNA fraction will bind only from ethanol concentrations of greater than 40%."

The Bastian et al. specification further states that in examples 2-8, the alcohol/salt mixtures were selected for the selective binding of single stranded nucleic acid. (column 10, lines 28-30) In particular, in example 2, single stranded nucleic acid was contacted with binding reagent B4 (70% ethanol in water); in example 3, single stranded nucleic acid was contacted with an ethanol-containing lysis buffer, L5 (2.5 M GTC, 25 mM Na citrate, pH 7.5, 1% β-MSH, 30% ethanol) which served as the binding reagent; in example 4, single stranded nucleic acid was contacted with the binding reagent, B1 (ethanol); and in examples 5, 6, 7 and 8, single stranded nucleic acid was contacted with binding reagent B4 (70% ethanol in water).

Examples 9 and 10 of the Bastian et al. specification describe the selective binding of double stranded nucleic acid to a solid support without a binding reagent and examples 11 to 13 describe the separation of single stranded nucleic acid and double

stranded nucleic acid from the same cell lysate. Specifically, in example 11, double stranded nucleic acid was first bound to a solid support in the presence of lysis buffer, L8, and the remaining single stranded nucleic acid was bound to a solid support in the presence of binding reagent B4 (70% ethanol in water). In example 12, single stranded nucleic acid was first bound to a solid support in the presence of binding reagent B4 (70% ethanol in water) and the remaining double stranded nucleic acid was bound to a solid support in the presence of binding reagents B1 (ethanol) and B5 (5.9 M GTC). Finally, in example 13, both single stranded nucleic acid and double stranded nucleic acid were bound to a solid support in the presence of binding reagent B1 (ethanol) and the double stranded nucleic acid was eluted from the support with washing buffer W5 (0.5 M GTC, 25 mM TRIS/HCl, pH 7.5, 10% ethanol) while the single stranded fraction remained bound.

Thus all of the enabling teachings in the Bastian et al. patent are directed to methods of separating single stranded nucleic acid from double stranded nucleic acid by contacting the single stranded nucleic acid with a material containing alcohol groups and there is no enabling support in the Bastian et al. patent for a method of separating single stranded nucleic acid from double stranded nucleic acid by contacting single stranded nucleic acid with a binding reagent in the absence of a material containing alcohol groups.

The language of the allowed claims of the Bastian et al. patent further supports applicants' position in this regard. In particular, claim 1, the broadest and only independent claim of the Bastian et al. patent, recites a process for the separation of single-stranded nucleic acid from double-stranded nucleic acids by treatment of a biological source, thereof, said treatment comprising the steps of:

a) applying to a first mineral support an aqueous solution containing a sample of said source under conditions whereby said first mineral support adsorbs only one of said

single- or double-stranded nucleic acids followed by, optionally, washing said first mineral support; and

b) applying to a second mineral support the other of said single-or double-stranded nucleic acids, which was not adsorbed by the first mineral support, in an aqueous solution containing materials with alcohol groups. (Emphasis added).

Thus, the invention described in the Bastian et al. patent, as represented by the claims of that patent, sets forth the requirement that the reagents used to separate single stranded nucleic acid from double stranded nucleic acid present in a mixture of the two nucleic acid types include materials that contain alcohol groups. There is no enabling disclosure anywhere in the Bastian et al. patent of a method of separating single stranded nucleic acid from double stranded nucleic acid by using reagents to bind single stranded nucleic acid to a solid support wherein the reagents lack materials containing alcohol groups.

Claims 16, 38 and 44 are amended herein to recite a method for separating single stranded nucleic acid from double stranded nucleic acid, comprising the steps of:

contacting a mixture comprising both single stranded nucleic acid and double stranded nucleic acid with a first liquid comprising a chaotropic agent and a nucleic acid binding solid phase in the absence of material containing alcohol groups, wherein the first liquid has a composition such that the double stranded nucleic acid binds to the solid phase;

separating the solid phase from a supernatant containing the single stranded nucleic acid; and

contacting the supernatant with a second liquid comprising a second nucleic acid binding solid phase, in the presence of a chaotropic agent (and a chelating agent as in claim 44 or a chelating agent and divalent positive ions as in claim 38) and in the absence of material containing alcohol groups, wherein the second liquid has a composition such

that the resulting mixture of supernatant and second liquid allows for binding of the single stranded nucleic acid to the second solid phase.

Support for these amendments can be found in the language of the original claims and in the teachings of the specification. Specifically, the limitation that the double stranded nucleic acids in the mixture are contacted with a liquid in the absence of material containing alcohol groups and that the single stranded nucleic acids in the supernatant are contacted with a second liquid in the absence of material containing alcohol groups is supported in the teachings throughout the instant specification of a method for separating single stranded nucleic acids and double stranded nucleic acids in a mixture which describes the use of reagents that are not composed of material containing alcohol groups. Thus, this limitation finds implicit support in the specification based on the teachings of what the claimed invention is and therefore, also implicitly, what the invention is not.

It is stated in the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement as published on January 5, 2001 in the Federal Register (Vol. 66, pages 1099-1111) that "[w]hile there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." (page 1105, first column). Thus, the written description requirement can properly be met by implicit disclosure of what an invention is not on the basis of the description of what the invention is and it would be clear to one skilled in the art that the present applicants were in possession of the invention as now claimed, i.e., a method for isolating single stranded nucleic acid and double stranded nucleic acid in a mixture by using binding reagents that contain no materials with alcohol groups.

Thus, applicants believe claims 16, 38 and 44 as amended are adequately supported by the instant specification and respectfully request entry of these amended

claims into the present application. On the basis of applicants' comments above regarding the absence in the Bastian et al. patent of any supporting disclosure of a method of isolating single stranded nucleic acid and double stranded nucleic acid in a mixture by using reagents that lack materials containing an alcohol group, it is believed that the claims as amended are free from the cited art. Thus, applicants respectfully request the withdrawal of this rejection and allowance of the pending claims to issue.

For the foregoing reasons, applicants believe that all of the pending rejections have been adequately addressed and that the claims as presented are in condition for allowance. The Examiner is encouraged to contact the undersigned directly if such contact will expedite the examination and allowance of the pending claims.

No fee is believed due. However, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,

Mary L. Miller
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Customer No.

20792
PATENT TRADEMARK OFFICE

CERTIFICATE OF EXPRESS MAILING

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Date of Deposit: January 6, 2003

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to Commissioner of Patents, Washington, DC 20231.

Anthony P. DeRosa
Date of Signature: January 6, 2003

APPENDIX
Marked-up Version Showing Changes Made

16. (Twice amended) A method for separating single stranded nucleic acid from double stranded nucleic acid, comprising the steps of:

contacting a mixture comprising both single stranded nucleic acid and double stranded nucleic acid with a first liquid comprising a chaotropic agent and a nucleic acid binding solid phase in the absence of material containing alcohol groups, wherein the first liquid has a composition such that the double stranded nucleic acid [preferentially] binds to the solid phase;

separating the solid phase from a supernatant containing the single stranded nucleic acid; and

[treating] contacting the supernatant with a second liquid comprising [a chaotropic agent and] a second nucleic acid binding solid phase, in the presence of a chaotropic agent and in the absence of material containing alcohol groups wherein the second liquid has a composition such that the resulting mixture of supernatant and second liquid allows for binding of the single stranded nucleic acid [material] to the second solid phase[, whereby the single stranded nucleic acid is isolated].

38. (Amended) A method for separating single stranded nucleic acid from double stranded nucleic acid, comprising the steps of:

contacting a mixture comprising both single stranded and double stranded nucleic acid with a first liquid comprising a chaotropic agent and a nucleic acid binding solid phase in the absence of material containing alcohol groups, wherein the first liquid has a composition such that the double stranded nucleic acid [preferentially] binds to the solid phase;

separating the solid phase from a supernatant containing the single stranded nucleic acid; and

[treating] contacting the supernatant with a second liquid comprising [a chaotropic agent, a chelating agent, and divalent position ions and] a second nucleic acid binding solid phase, in the presence of a chaotropic agent, a chelating agent and divalent positive ions and in the absence of material containing alcohol groups, wherein the second liquid has a composition such that the resulting mixture of supernatant and second liquid allows for binding of the single stranded nucleic acid [material] to the second solid phase[, whereby the single stranded nucleic acid is isolated].

44. (Amended) A method for separating single stranded nucleic acid from double stranded nucleic acid, comprising the steps of:

contacting a mixture comprising both single stranded nucleic acid and double stranded nucleic acid with a first liquid comprising a chaotropic agent and a nucleic acid binding solid phase in the absence of material containing alcohol groups, wherein the first liquid has a composition such that the double stranded nucleic acid [preferentially] binds to the solid phase;

separating the solid phase from a supernatant containing the single stranded nucleic acid; and

[treating] contacting the supernatant with a second liquid comprising [a chaotropic agent, divalent positive ions and] a second nucleic acid binding solid phase, in the present of a chaotropic agent and divalent positive ions and in the absence of material containing alcohol groups, wherein the second liquid has a composition such that the resulting mixture of supernatant and second liquid allows for binding of the single stranded nucleic acid [material] to the second solid phase[, whereby the single stranded nucleic acid is isolated].